FORM PTO-1390 (REV 10-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: CU-2642 RJS

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/936470

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/RU99/00320	06 September 1999	16 March 1999

TITLE OF INVENTION: ANTIVIRAL AGENT IN THE FORM OF NOSEDROPS

APPLICANT(S) FOR DO/EO/US: Petr Jakovlevich GAPONJUK et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. [X] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [X] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment. with new claims 6-13
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

Express Mail Label No.:

L 698 182394

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	531 Rec'd PC...	ATTORNEY'S DOCKET NUMBER
09/936,4[illegible]	PCT/RU99/00320	13 SEP 2001	CU-2642 RJS

	CALCULATIONS PTO USE ONLY	
17. [X] The following fees are submitted:		
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	8 - 20 =	0	X **$18.00**	$	
Independent claims	1 - 3 =	0	X **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1000.00	
[X] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 500.00	
SUBTOTAL =				$ 500.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 500.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $ 500.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 12-0400. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Ladas & Parry
224 South Michigan Avenue
Suite 1200
Chicago, Illinois 60604
(312) 427-1300

SIGNATURE:

Richard J. Streit

NAME

25765

REGISTRATION NUMBER

September 13, 2001

DOCKET: CU-2642

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT: Petr Jakovlevich GAPONJUK et al)
)
TITLE: ANTIVIRAL AGENT IN THE FORM OF NOSE DROPS)
)
COMPLETION OF PCT/RU99/00320 filed 06 September 1999)

The Commissioner for Patents (DO/EO/US)
Box PCT
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Please amend the application being filed herewith under 35 USC 371.

IN THE CLAIMS:

Please cancel claims 1-5 from the PCT application as filed and substitute the clean version of new claims 6-13 as attached herewith.

REMARKS

The aforesaid claims are based on the claims as filed, with amendments to place the same in better condition for examination under U.S. rules of practice.

Respectfully submitted,

September 13, 2001
Date

Attorney for Applicant

Richard J. Streit, Reg. 25765
c/o Ladas & Parry
224 South Michigan Avenue
Chicago, Illinois 60604
(312) 427-1300

Claims

6. An antiviral liquid drug presented as nasal drops comprising an interferon and a biocompatible polymer wherein the interferon component is a genetically engineered interferon alpha, beta or gamma, and the drug viscosity is 11 - 300 Pa*s.

7. The antiviral drug of claim 6, further comprising an antioxidant.

8. The antiviral drug of claim 7, wherein the interferon, biocompatible polymer and antioxidant are contained in the following amounts per ml buffer mixture:

Genetically engineered interferon 1,000 - 500,000 IU

Biocompatible polymer 0.005 - 0.714 g

Antioxidant 0.0001 - 0.0008 g

9. The antiviral drug of claim 7, wherein the antioxidant is Trilon B.

10. The antiviral drug of claim 7, wherein the biocompatible polymer is polyvinilpyrrolidone.

11. The antiviral drug of claim 7, wherein the biocompatible polymer is polyethylene oxide.

12. The antiviral drug of claim 7, wherein the biocompatible polymer is a combination of poylvinilpyrrolidone and polyethylene oxide.

13. The antiviral drug of claim 12, wherein the polyvinilpyrrolidone to polyethylene oxide ratio is 1:1 to 1:50.

ANTIVIRAL AGENT IN THE FORM OF NOSE DROPS

FIELD OF THE INVENTION

The present invention can be used in pharmacology specifically in the preparation of interferon-containing compositions, which are capable of conserving their biological activity and can be administrated intranasally, e.g. in the preparation of nasal drops.

BACKGROUND OF THE INVENTION

Medicines containing interferons (natural, recombinant or genetically engineered) are widely used. Interferon-containing preparations, in addition to antiviral effects, cause strong immunomodulatory effects that induce several positive homeostatic shifts, antitumour effects, etc. (RU, Application 940942742 Cl. A 61 K 38/21, 1997. RU, patent 20957544, Cl. A 61 K 38/21, 1996).

In Russia, natural human interferons derived from leukocytes has been widely used for the treatment and prevention of influenza and acute viral respiratory infections (AVRI) since the late 1960s. This interferon was manufactured from expensive donor blood leukocyte preparations (RU, Patent 2033180, Cl. A 61 K 38/21, 1995. SU, Inventor's Certificate 297296, Cl. A 61 K 36/21, 1977. RU, patent 2108804, Cl. A 61 K 38/21, 1996).

Medicines prepared from leukocytes or any other component of human blood are potentially hazardous and can transmit viral infection (hepatitis, herpes virus, cytomegalovirus, AIDS, slow infections etc.).

Because of this, recombinant and genetically engineered interferon preparations of the highest purification (up to 98% pure) are increasingly used for clinical purposes (FS 42-3279-96, VFS 42-2989-97, RU, Patent 2073522, Cl. A 61 38/21, 1997. *Ershov, F.I., Sistema interferona v norme i pri patologii* (The Interferon System under Normal and Pathological Conditions), Moscow: Medicina, 1966, p.216.

These preparations are effective in treating oncological diseases by parenteral administration of high doses (3 - 10 million IU or more per 24 h) in repeated long courses. However, such doses often cause side effects, such as disorders haemopoiesis, suppression of the immune system, formation of anti-interferon antibodies etc.

However, the recent experience with clinical administration of interferons suggests that their efficacy can be increased by using appropriate drug forms (with account taken of the specific pathogenetic features of the diseases) designed to deliver high concentrations of interferon to the focus of viral infection. After such an administration, interferon causes antiviral and immunomodulatory effects without cytostatic or other side effects. This makes it expedient to develop various drug forms containing interferons designed for topical administration (suppositories, ointments, drops, aerosols, etc.) The closest analogue of this invention, in terms of the nature of the drug and achieved result, is an antiviral drug form for intranasal administration containing human interferon, a biocompatible polymer (6% Polyglucin), and a buffer mixture with the following contents of ingredients per ml solution:

Interferon	(1-6.6).10 IU
Biocompatible polymer (Polyglucin)	5 - 30
Buffer mixture	pH 7.0 - 7.6 in

solution

(RU. Patent 2095081, Cl. A 61 K 38/21, 1977).

However, intranasal drug forms containing recombinant or genetically engineered interferons have not been developed in Russia.

SUMMARY OF THE INVENTION

The main idea of this invention was to develop of an antiviral drug form (nasal drops) containing a genetically engineered interferon, which would allow a prolonged contact with nasal mucous, act topically at the site of primary invasion and reproduction of influenza and other respiratory viruses, be easily absorbable, and have an optimal viscosity permitting the drug to spread over the mucous and be retained on it for a long time.

To solve this problem, we developed an antiviral drug (nasal drops) containing a liquid interferon preparation (a genetically engineered alpha, beta or gamma interferon with viscosity of (1.1 - 30.0) * 10 Pa*s). The antiviral drug contains a biocompatible polymer, antioxidant, and buffer mixture with the following contents of ingredients per ml buffer mixture:

Genetically engineered interferon	1000 - 50,000 IU
Biocompatible polymer	0.005 - 0.714 g
Antioxidant	0.0001 - 0.0008 g

Trilon B is used as an antioxidant, and polyvinilpyrrolidone and/or polyethylene oxide is used as biocompatible polymer. The drug described here contains

polyvinilpyrrolidone and polyethylene oxide at a ratio of 1:1 - 50.

DETAILED DESCRIPTION OF THE PREFFERED EMBODIMENTS

Variant 1. The technology of manufactured this drug (nasal drops) is the same for all variants describe below. Prepare solutions of the following ingredients in separate containers: 50% polyethylene oxide, 6% polyvinilpyrrolidone and 10% aqueous Trilon B. Filter the solutions. Use phosphate-buffered saline as a solvent/ Add these solutions to a manufacturing vessel in the specified sequence, and sterilize. Then add genetically engineered interferon. Mix the ingredients. Dispense the solution into appropriate containers, hermetically seal and label.

Suggested composition of the antiviral drug:

Each millilitre of the buffer mixture contains:

Genetically engineered interferon beta	500,000 IU
Polyvinilpyrrolidone	0.014 g
Polyethylene oxide	0.7 g
Trilon B	0.0008 g
Viscosity of solution	30.0*10 Pa*s

Variant 2. Proceed as described under Variant 1.

Suggested composition of the antiviral drug:

Each millilitre of the buffer mixture contains:

Genetically engineered interferon alpha	10,000 IU
Polyvinilpyrrolidone	0.01 g
Polyethylene oxide	0.1 g
Trilon B	0.0004 g
Viscosity of solution	3.0*10 Pa*s

Variant 3. Proceed as described under Variant 1.

Suggested composition of the antiviral drug:

Each millilitre of the buffer mixture contains:

Genetically engineered interferon gamma	1,000 IU
Polyvinilpyrrolidone	0.05 g
Trilon B	0.0001 g
Viscosity of solution	1.1*10 Pa*s

REASIBILITY OF INDUSTRIAL-SCALE MANUFACTURE

The antiviral drug (nasal drops) obtained as described in the previous section has the appearance of a clear liquid whose viscosity differs between variants. Laboratory tests performed on cultured animal cells showed that the drug is not toxic and fully conserves its antiviral activity.

Clinical tests on 59 volunteers of 18-20 years showed that the drug is safe, well-tolerated, and does not induce the formation of anti-interferon antibodies. It is administrated in nasal drops for treating acute respiratory disease and influence. For prophylaxis of respiratory diseases, the drug is administrated intranasally two times a day (2-3 drops into each nostril) during the whole period of contact with a patient (each drop is equivalent to 500 IU). For the treatment of influenza, the drug is administrated at dose of 2-3 drops into each nostril every 3-4 hours for 5 days.

Claims

1. An antiviral liquid drug presented as nasal drops containing interferon, wherein: (a) the interferon component is a genetically engineered interferon alpha, beta or gamma; and (b) the drug viscosity is (1.1 - 30.0) * Pa*s.

2. The antiviral drug of claim 1, wherein the active substance, biocompatible polymer and antioxidant are contained in the following amounts per ml buffer mixture:

Genetically engineered interferon	1,000 - 300,000 IU
Biocompatible polymer	0.005 - 0.714 g
Antioxidant	0.0001 - 0.0008 g.

3. The antiviral drug of claim 1, wherein the antioxidant is Trilon B.

4. The antiviral drug of claim 1, wherein the biocompatible polymer(s) is (are) polyvinilpyrrolidone and/or polyethylene oxide.

5. The antiviral drug of claims 1 - 4, wherein the polyvinilpyrrolidone-to-polyethylene oxide ratio is 1:1 - 50.

Docket: CU-2642

PATENT

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: *(check one applicable item below)*

- ☐ original
- ☐ design
- ☐ supplemental

Note: If the Declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.

- ☒ national stage of PCT

Note: If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR CIP.

- ☐ divisional
- ☐ continuation
- ☐ continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

ANTIVIRAL AGENT IN THE FORM OF NOSE DROPS

SPECIFICATION IDENTIFICATION

the specification of which: *(complete (a), (b) or (c))*

☐ (a) is attached hereto.

☐ (b) was filed on _____ as ☐ Serial No. _____ or
☐ Express Mail No. *(as Serial No. not yet known)* _____
and was amended on _____ *(if applicable).*

Note: Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the Declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental Declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 CFR 1.67.

☒ (c) was described and claimed in PCT International Application No. PCT/RU99/00320 filed on 06 September 1999.

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, § 1.56,

(also check the following items, if desired)

☐ and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

☐ in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 CFR 1.98.

PRIORITY CLAIM (35 U.S.C. § 119(a)-(d))

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

☐ (d) no such applications have been filed.

☒ (e) such applications have been filed as follows.

Note: Where item (c) is entered above and the international application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. § 119(a)-(d)

COUNTRY (OR INDICATE IF PCT	APPLICATION NUMBER	DATE OF FILING (day/month/year)	PRIORITY CLAIMED UNDER 35 USC 119
Russia	99100666	16 March 1999	☒ YES NO ☐
			☐ YES NO ☐

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S) (35 U.S.C. § 119(e))

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

Note: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CIP APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. § 120.

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith *(list name and registration number)*.

Thomas F. Peterson, 24790; Richard J. Streit, 25765; Donald P. Reynolds, 26220; W. Dennis Drehkoff, 27193; Vangelis Economou, 32341; Brian W. Hameder, 45613; Valerie Neymeyer-Tynkov, Reg. 46956; Paul B. West, 18947; Joseph H. Handelman, 26179; Peter D. Galloway 27885; John Richards, 31503; Iain C. Baillie, 24090; Richard P. Berg, 28145

☐ Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE TO:

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DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

(312) 427-1300

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Note: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other documents.

Full name of first joint inventor

Petr (Given Name) Jakovlevich (Middle Initial or Name) GAPONYUK (Family (or Last) Name)

Inventor's signature [signature]

Date 06.12.01 **Country of Citizenship** Russia

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Post Office Address 121433, 7-58, Malaya Filevskaya st., Moscow, Russia

200

Full name of second joint inventor

Elena (Given Name) Alexeevna (Middle Initial or Name) MARKOVA (Family (or Last) Name)

Inventor's signature

Date 20.10.2001 **Country of Citizenship** Russia

Residence Melbourne, Australia AUX

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300

Full name of third joint inventor

Iliya (Given Name) Alexandrovich (Middle Initial or Name) MARKOV (Family (or Last) Name)

Inventor's signature

Date 15.10.2001 **Country of Citizenship** Russia

Residence Moscow, Russia RUX

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